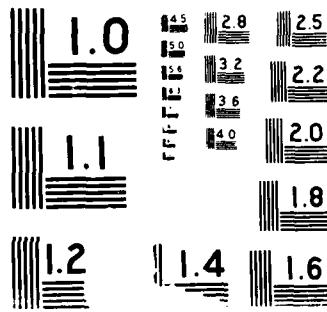


AD-A194 587 NEW SYNTHETIC APPROACHES TO TAT(U) BONN UNIV (GERMANY F 1/1  
R) H WAMHOFF 27 AUG 87 DAJA45-85-C-0016

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"New Synthetic Approaches to TAT"

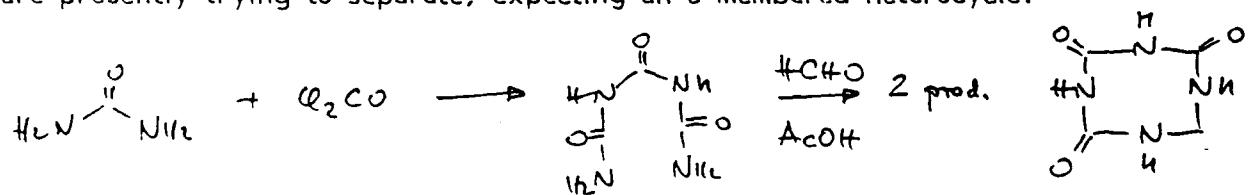
✓ **Sixth Interim Report (Item 0006)**

In continuation and implementation of my recent travel & conference report dated July 24, 1987, we are still following up our three general synthetic strategies for developing new approaches to TAT:

- (a) ring synthetic methods from small molecules
- (b) partially destructed hexamethylenetetramine (DAPT)
- (c) tetra- and hexamerization of methyleneimines in the presence of metal ions.

A recent method (Dusemund & Schurreit, Arch.Pharm. (Weinheim) 319, 826 (1986)). to cyclize sulfonylurea in TFA to afford 1,5,2,4,6,8-dithiatetrazocine-1,1,5,5-tetroxide, proved to be not transferable to simple urea + TFA and only polymeric material has been formed; in a similar way, methylenediamine sulfate (nearly irreproducible) reacted with formaldehyde to give a complex mixture of decomposition products. The previously reported tetramerization of acetamide and formaldehyde gave only traces of TAT, detectable by TLC, but no isolation nor optimizing of the yield was possible.

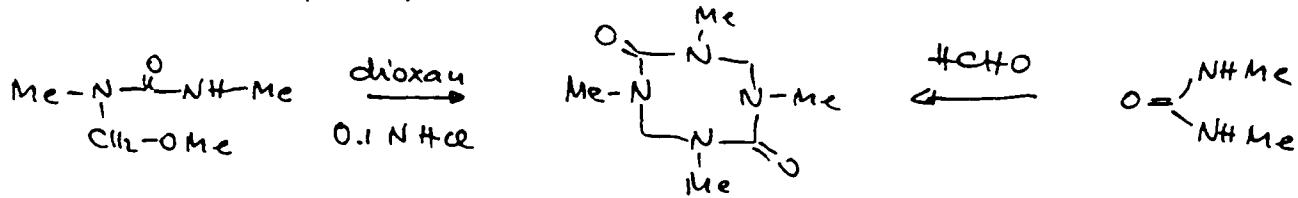
However, treatment of urea with phosgene led to a carbonyl-bridged bisureide which in turn was treated with formaldehyde to give a mixture of 2 products, which we are presently trying to separate, expecting an 8-membered heterocycle:



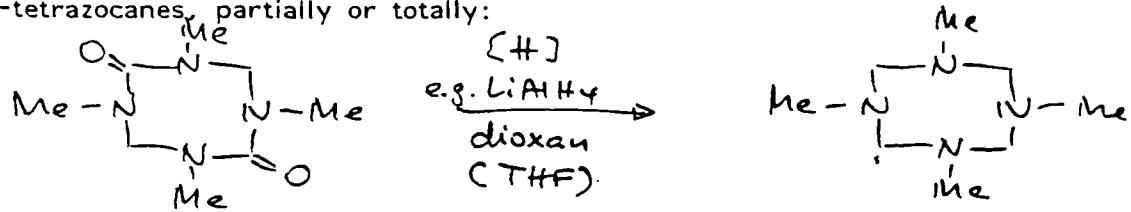
As shown by H. Petersen in his review (Synthesis 1973, 243) simple approaches to dioxo-tetrazocanes can be easily performed by  $\alpha$ -ureidoalkylation. Thus, 2,6-dioxo-

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1,3,5,7-tetramethyloctahydro-1,3,5,7-tetrazocane is made as follows:

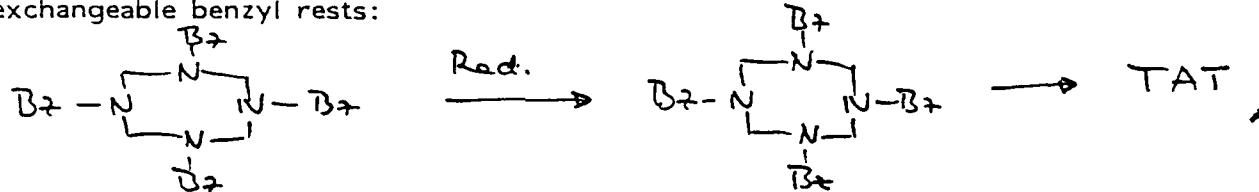


Similarly, N,N'-dimethylurea gives with formaldehyde the same compound (Kadowaki, Bull. Chem. Soc. Japan 11, 248 (1936). - This work could be nicely reproduced, and now we are consequently studying appropriate methods of reducing the obtained dioxo-tetrazocanes partially or totally:

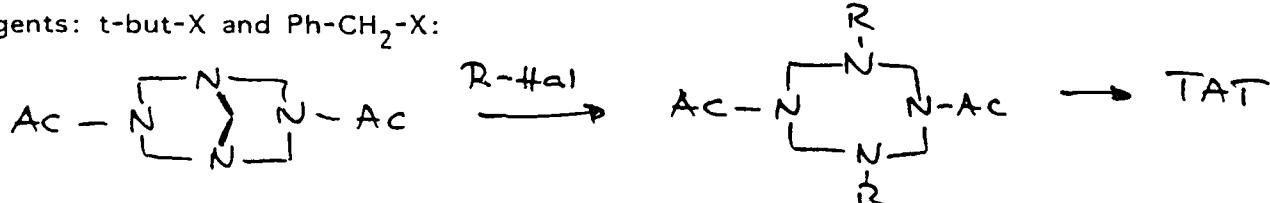


In the first orienting experiments,  $\text{LiAlH}_4$  turned out to be an unsufficient reagent, as in dioxane no reaction could be observed, but the reduction experiments are continued changing solvents and conditions; furthermore, other promising reductive agents are tried, as e.g. borane-dimethylsulfide or borane-THF (Brown et al. Synthesis 1981, 441, 996), or  $\text{Et}_3\text{O}^+\text{BF}_4^-/\text{NaBH}_4/\text{EtOH}$  (Borch, Tetrahedron Lett. 1968, 61), or trichlorosilane (Nagata et al. Chem. Lett. 1972, 989; Benkeser et al. J. Organomet. Chem. 178; 21 (1979)).

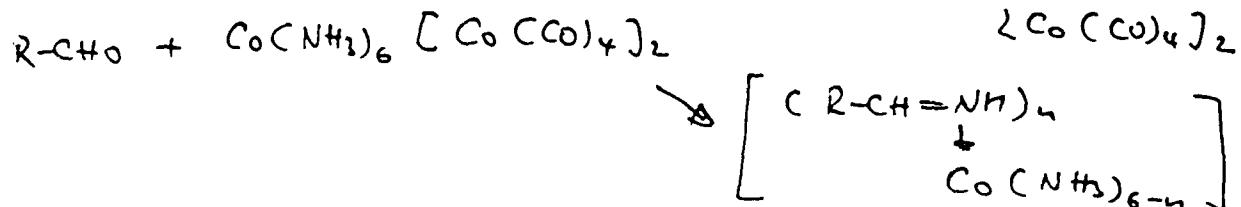
Synthesis and reduction will be further extended to benzylureas with its easily exchangeable benzyl rests:



Further experiments are carried out for destructing the methylene bridge in DAPT with suitable reagents; after I had an intense literature exchange with Dr. E.E. Gilbert (now consultant to Picatinny Areal), further approaches consist of removing the  $\text{CH}_2$ -bridge by oxidizing agents, such as  $\text{Cu}^{2+}$ ,  $\text{K}_3[\text{Fe}(\text{CN})_6]$ ,  $\text{Hal}_2\text{PPh}_3$ , but also by means of  $\text{AgNO}_3$  and  $\text{AgNO}_2$  (Lit.: Bernardi et al. J. Chem. Soc., Chem. Commun. 1974, 690), and by alkylation according to Agadzhanyan et al. Arm. Khim. Zh. 38, 274 (1985); Chem. Abstr. 103, 87853x (1985). - We want to prove the following alkylation agents: t-but-X and  $\text{Ph}-\text{CH}_2-\text{X}$ :



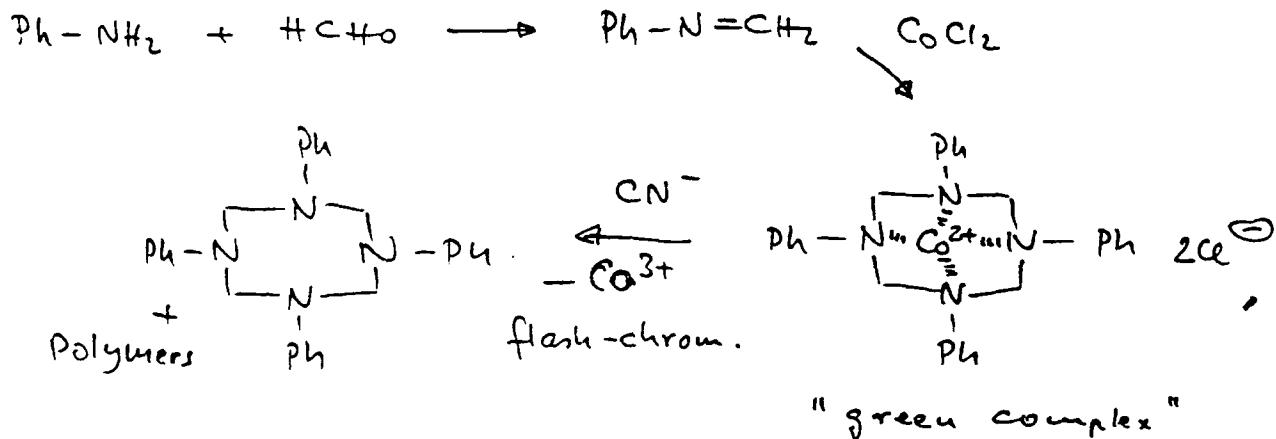
Regarding the Template-assisted tetra- and oligomerization of methyleneimines, we have found in the literature a mild and novel synthesis via Co-carbonyl complexes (Rhee et al., Tetrahedron Lett. 1970, 3419) employing the following typical complex:



The special improvement of this method lies in the complex stabilization of the imine, although working with the hazardous Co-carbonyls is a disadvantage.

Much work has been investigated so far to bring clearness into the promising but still hardly to repeat "Roumanian approach" (lit. cf. earlier reports), where aniline and formaldehyde are reacted in the presence of  $\text{CoCl}_2$  as template reagent. Depending on the conditions applied several cyclic oligomers are claimed to be formed, and all of them are of great interest being close analogs of TAT. - Although we have been able to detect the tetraphenyltetrazocane molecular peak by MS, the reproduction of the described Roumanian procedure turned out to be still difficult, as the individual descriptions and procedures are far too inaccurate.

Under progress now: the "green complex" is especially purified, before further demetallation is attempted with the aid of  $\text{CN}^-$  in suitable solvents:



Synthesis of the corresponding 12-membered ring is furthermore tried, and the synthesis seems to be much easier to reproduce; by this means we expect to have a comparison sample at hand to study stability, structure (X-ray?) and properties, which can be then transferred also to the 8-membered tetrazocane.

Heinrich Wamhoff  
Professor Dr. Heinrich Wamhoff

Contractor



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